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Abstract

Background: Preemptive genotyping is a strategy that tests for multiple pharmacogenomic variants before a drug is prescribed. Pharmacogenomic information currently appears in 165 FDA-approved drug labels, and many medications have FDA boxed warnings and/or available Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines that recommend action, such as selecting a different drug or dose, in patients with certain genotypes if the genetic test result was available. However, the implementation of established pharmacogenomic guidance is hardly done in clinical practice due to the lack of a clear population to genotype. Cardiac catheterization laboratory patients serve as a reasonable population due to their multiple comorbidities and increased likelihood of being on genetically actionable drugs. The objective of this study was to retrospectively assess the projected number of actionable pharmacogenetic-guided interventions that could have resulted with preemptive genotyping within a six-month time period for cardiac catheterization laboratory patients.

Methods: This single-center, retrospective study of an established cohort included 183 patients referred for coronary angiography between September 2012 and February 2014 at UNC Hospitals. A list of 20 drugs with genetically actionable FDA boxed warnings and/or CPIC guidelines was established a priori to guide medication collection. For these drugs, the relevant genes are *HLA-B, CYP2C19, CYP2D6, CYP2C9, SLCO1B1, VKORC1/CYP2C9,* and *DYPD*. Medication information was collected at discharge and at first follow-up. The primary endpoint was the projected number of genotype-guided interventions at discharge or first follow-up that could have occurred using published allele frequencies to estimate the projected presence of at-risk genotypes. Secondary endpoints included the distribution of total interventions by gene in the study population, and the projected annual number of genotype-guided interventions at discharge or first follow-up in the UNC catheterization laboratory patient population.

Results: The study population included 122 patients who had a first follow-up visit within 180 days of the catheterization. Patients were on average 63 years old, 57% male, and 73% Caucasian. Comorbidities included depression (13.9%), hyperlipidemia (63.9%), and heart failure (17.2%). Approximately 38% of patients underwent a percutaneous coronary intervention during the catheterization procedure. The most prevalent genetically actionable drugs at discharge or first follow-up were clopidogrel (48.4%), antidepressants (20.5%), simvastatin (13.9%), and warfarin (9.0%). Corresponding at risk genotypes of interest and projected frequencies were *CYP2C19* intermediate or poor metabolizers (28.9%) for clopidogrel, *CYP2C19* ultra-rapid or poor metabolizers (32.5%) for antidepressants, *SLCO1B1 C* allele carriers (23.6%) for simvastatin, and *VKORC1/CYP2C9* sensitive or highly sensitive responders (38.3%) for warfarin. The total projected number of genotype-guided interventions at discharge or first follow-up in the study population was 32. Distribution of total interventions by gene was as follows: 71.9% *CYP2C19*, 12.5% *SLCO1B1*, 12.5% *VKORC1/CYP2C9*, and 3.1% *CYP2C9*. Assuming each intervention is unique to one patient, a genotype-guided medication intervention could have been made in 26.2% (32 of 122) of the study population within 6 months of their presentation to the cardiac catheterization laboratory. When carried out to the annual UNC Catheterization Laboratory population, the total projected number of genotype-guided interventions at discharge or first follow-up increased to 565.

Conclusions: A preemptive genotyping strategy with a multi-gene panel in cardiac catheterization laboratory patients would result in genotype-guided interventions in approximately 1 out of every 4 patients. Almost 30% of interventions involved non-*CYP2C19* drugs, suggesting the potential benefit of a multiplexed genotyping approach that extends beyond *CYP2C19* testing.

Introduction

Genetically guided personalized medicine has become more clinically significant in recent years, and the US Food and Drug Administration (FDA) is reflecting these new findings in its drug evaluation and approval process. In 2005, the FDA issued a comprehensive pharmacogenomics guidance document addressing how and when drug development entities should submit genomic data to the FDA.[1] Since then, pharmacogenomic information has appeared in 165 FDA-approved drug labels.[2] Without taking into account oncology drugs, which are oftentimes exceedingly complex to dose and administer, there are currently 7 medications with genomic-associated black box warnings, 41 with either published Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines or FDA label recommendations influencing drug dosing and selection, and numerous more categorized as genetically "actionable" with implications on adverse drug outcomes such as toxicities, side effects, and therapy failures. Over 30 of these medications are listed in the Top 200 Drugs of 2012 article published by Pharmacy Times.[3] Despite this, genetic information is not routinely obtained and the implementation of genotype-guided drug regimens into the standard of care remains a subject of ongoing investigation and debate. Due to the substantial impact pharmacogenomics could have on health outcomes, there is an increasing need to open new avenues for translating and applying it into clinical practice.

Traditionally, pharmacogenetic testing is done for genetic variations the affect drug response when therapy is initiated for patients. This approach is reactive in that the decision to order the test is made alongside or after the decision to initiate therapy. Often, genotyping patients retrospectively only provides pharmacogenetic information pertinent to the specific drug in question and cannot be applied to future therapeutic decisions involving agents affected by different genes. Furthermore, significant barriers currently exist, limiting consistent and widespread adoption in everyday clinical practice. These barriers include cost, and lack of capability or long turnaround times at most institutions. However, advances in genetic testing methodologies have allowed a single genetic test to interrogate multiple genes simultaneously. This advancement in technology, coupled with its competitive pricing, has the potential to shift genotyping decision making from a traditional, reactive strategy to one that is proactive. Preemptive genotyping is a strategy that tests for multiple pharmacogenomic variants before a drug is prescribed, allowing patient genetic information to be stored for later use. The information obtained from this genotyping approach can be particularly beneficial to practitioners when prescribing a wide range of current and future medications, especially if these therapies come with boxed warnings warranting genetic testing or CPIC and other genome-based dosing guidelines. Importantly, preemptive genotyping eliminates barriers associated with turnaround time and allows the clinician to focus on how to best implement this data into patient care instead of deciding whether the test should be ordered or not. Moreover, the unfamiliarity of this material can create more opportunities for pharmacists in contributing to both the therapeutic decision-making and educational process by interpreting and relaying pharmacogenomic information to providers and patients. Lastly, preemptive genotyping, unlike reactive genotyping, allows for genetic information to be readily available in situations where a clinical decision or treatment cannot be deferred. Overall, preemptive genotyping could be an effective method of implementing pharmacogenomic data in practice and potentially prevent adverse drug-gene interactions and subsequent hospital admissions, which can be costly to patients and providers alike.

Despite its promising outlook, preemptive genotyping still faces challenges preventing widespread adoption. To improve the implementation of preemptive genotyping, it is essential to first identify a target population where preemptive genotyping would provide maximum clinical benefit and evaluate

its projected impact on drug selection and dosing. Cardiac catheterization laboratory patients may be ideal candidates as these individuals often have multiple comorbidities, increasing their likelihood of being on or being initiated on multiple pharmacologic therapies in which genetic testing is recommended.[4] For instance, approximately one-third of these patients will have a stent placement, a procedure in which testing for the *CYP2C19* genotype is recommended prior to starting the patients on the anti-platelet agent, clopidogrel. This is due to the diminished effectiveness of the drug in patients with certain loss-of-function polymorphisms of the gene, which can lead to failure of therapy and potentially fatal cardiovascular events. Other drugs with pharmacogenomic information their labels commonly seen with cardiac catheterization laboratory patients include anti-platelet and anti-thrombotic agents, beta blockers, anti-depressants, statins, and pain relievers.[4] To our knowledge, there are no studies currently published evaluating the use of preemptive genotyping in this patient population.

Additionally, it is crucial to determine which parameters would be clinically significant in the implementation of an established pharmacogenetic guidance. We defined medications as "genetically actionable" if they have an FDA boxed warning and/or available Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline that recommend action, such as selecting a different drug or dose, in patients with certain genotypes if the genetic test result was available.

The purpose of this study was to retrospectively assess the projected number of actionable pharmacogenetic-guided interventions that could have resulted with preemptive genotyping within a 6 month time period for cardiac catheterization laboratory patients

Methods

Patient population

This was a single-center, retrospective cohort study of 183 UNC Cardiac Catheterization Laboratory patients recruited between September 2012 and February 2014.[5] An institutional review board approved this study. Patients aged 18-80 years who were referred for coronary angiography and consented to participation in a DNA biorepository were included. Patients with one or more of the following conditions were excluded: severe concurrent illness, systemic inflammatory disease, malignancy actively being treated, ST-elevation myocardial infarction (STEMI), end-stage liver disease (ESRD) with or without dialysis, systemic immunosuppressive medication use, hematological disorder affecting platelet function, prior heart transplantation, hematocrit <30%, and pregnancy.

Medication selection

A literature and database review of the Food and Drug Administration's Table of Pharmacogenomic Biomarkers in Drug Labeling and PharmGKB was conducted. Drugs with pharmacogenomic information in their FDA labeling were documented (see Table 7). Oncology, immunomodulary, and specialty drugs such as ivacaftor were not evaluated due to the biorepository exclusion criteria. The list was subsequently narrowed down to only include drugs with actionable pharmacogenomic recommendations and high CPIC levels of evidence (A or B). The final list of medications to collect included 20 drugs with genetically actionable FDA boxed warnings and/or CPIC guidelines.

Data collection

Patient demographics, clinical information, and medication use were abstracted from EPIC, the electronic medical record. Medication information was collected at discharge and at the first follow-up clinic visit or hospitalization after the catheterization procedure and subsequently documented as nominal (yes/no) variables at each time point.

Outcome measures

The primary endpoint was the projected number of genotype-guided interventions in the study population at discharge or first follow-up that could have occurred if genotype information was available at the time of patient encounter. Secondary endpoints included the distribution of total interventions by gene in the study population, and the projected annual number of genotype-guided interventions at discharge or first follow-up in the UNC catheterization laboratory patient population.

Calculations and analysis

Drug prevalence at discharge or first follow-up was calculated using descriptive statistics. Projected genotype frequencies for 7 genes at risk for actionable pharmacogenetic recommendations (*HLA-B, CYP2C19, CYP2D6, CYP2C9, SLCO1B1, VKORC1/CYP2C9,* and *DYPD*) were estimated based on published literature for Caucasian-dominated populations from CPIC supplements[5,7-13] and, in the case of *VKORC1/CYP2C9*, the ENGAGE AF-TIMI 48 study.[12] When only a genotype frequency range was provided for *CYP2D6* genetic variants and *DYPD* partial DPD deficiency, the upper and lower bounds of the genotype frequency were averaged.[10,13] The Hardy-Weinberg equation was used to calculate at risk genotype frequencies when only allele frequencies were available, such as in the case of *SLCO1B1 C* and *HLA-B*1502* allele carriers.[8,11] The projected number of interventions for each drug was calculated by multiplying the observed drug frequency, projected at risk genotype frequency, and number of patients in the study population. The overall number of interventions was summed (see Table 4).

Results

A population of 183 patients from the UNC Cardiac Catheterization Laboratory who had donated blood samples to the biorepository were screened for inclusion. Forty-seven patients either had no follow-up in the UNC system or did not have medication records listed in their patient charts and were excluded from the analysis. An additional fourteen patients did not meet eligibility due to their first follow-up visit being greater than 180 days (see Figure 1).

Patient demographics

The study population included 122 patients who had a first follow-up clinic visit or hospitalization within 180 days of the catheterization procedure. Patients were on average 63 years old, 57% male, and 73% Caucasian. Comorbidities included obesity (50.8%), history of depression (13.9%), hyperlipidemia (63.9%), diabetes (33.6%), heart failure (17.2%), and hypertension (77.9%). Approximately 38% of patients underwent a percutaneous coronary intervention during the catheterization procedure and the mean first follow-up visit was 36 days (see Table 1).

Prevalence of genetically actionable drugs

The most prevalent genetically actionable drug at discharge or at first follow-up was clopidogrel (59 patients; 48.4%), followed by antidepressants (25 patients; 20.5%), simvastatin (17 patients; 13.9%), and warfarin (11 patients; 9.0%). Genetically actionable drugs with lower prevalence included allopurinol (3 patients; 2.5%), phenytoin (2 patients; 1.6%), and codeine (2 patients; 1.6%). No patients were on carbamazepine and fluorouracil either at discharge or at first follow-up (see Table 2).

At risk genotype frequencies

Corresponding at-risk genotypes of interest and projected Caucasian frequencies for the most prevalent genetically actionable drug at discharge or at first follow-up were CYP2C19 intermediate or poor metabolizers (28.9%) for clopidogrel, CYP2C19 ultra-rapid or poor metabolizers (32.5%) for antidepressants, SLCO1B1 C allele carriers (23.6%) for simvastatin, and VKORC1/CYP2C9 sensitive or highly sensitive responders (38.3%) for warfarin. The projected Caucasian at-risk genotype frequencies for CYP2D6 ultra-rapid, intermediate, or poor metabolizers was 15.5%. The projected Caucasian at-risk genotype frequencies for individuals with partial or full DPD deficiency was 4.2%. HLA-B*5801 and HLA-B*1502 allele carriers had projected Caucasian at-risk genotype frequencies of 0.8% and 0.01% respectively (see Table 3).

Projected genotype-guided interventions in study population

The total projected number of genotype-guided interventions at discharge or first follow-up in the study population was 32. The distribution of total genotype-guided interventions in the study population by gene was 71.9% for *CYP2C19*, 12.5% for *SLCO1B1*, 12.5% for *VKORC1/CYP2C9*, and 3.1% for *CYP2C9*. There were no projected interventions involving drugs actionable for *CYP2D6, HLA-B,* and *DYPD*. Assuming each intervention is unique to one patient, a genotype-guided medication intervention could have been made in 26.2% (32 of 122) of the study population within 6 months of their presentation to the cardiac catheterization laboratory (see Table 5 and Figure 2).

Projected annual genotype-guided interventions

When carried out to the annual UNC Catheterization Laboratory population of 2000 patients, the total projected number of genotype-guided interventions at discharge or first follow-up increased to 565. A total of 396 interventions involved *CYP2C19* drugs, 11 involved *CYP2C9*, 66 involved *SLCO1B1*, 69 involved *VKORC1/CYP2C9* and 23 involved *CYP2D6* drugs. The discretion between the number of projected *CYP2D6* genotype-guided interventions in the study population and the annual catheterization laboratory patients can be attributed to the how the interventions were calculated. Before the total number of interventions was summed, the calculated interventions were rounded as such: calculated intervention of greater than or equal to 0.5 was rounded up to 1 and calculated intervention less than 0.5 was rounded down to 0. With a higher patient population, the calculated *CYP2D6* related interventions that was originally rounded down are now showing up (see Table 6).

Discussion

This study found that a preemptive genotyping strategy in cardiac catheterization laboratory patients would result in a genotype-guided intervention in approximately 1 out of every 4 patients within 6 months of their presentation to the catheterization laboratory, which could optimize medication use in

accordance with FDA boxed warnings and CPIC guideline recommendations. We arbitrarily chose the 6 month time window for our analysis as a means of estimating the immediate number of genotype-guided interventions that could be made. The high prevalence of genetically actionable drugs during this short period of time serves as compelling evidence to implement pharmacogenomic testing in this population. Additionally, as almost 30% of interventions involved non-*CYP2C19* drugs, the potential benefit of a multi-gene panel that extends far beyond just *CYP2C19* testing.

One of the study's limitations was it's a small sample size, which puts the generalizability of the results into question. However, the characteristics of cohort of patients are comparable to that of the general catheterization laboratory population, according to patient data for 2014 that was reported in four National Cardiovascular Data Registries.[15] Actionable oncology and immunomodulatory drugs were not assessed in this study per the patient exclusion criteria, due to the complexity of treatment regimens in patients with active cancers or inflammatory conditions. Thus, the results of this study should not be applied to this patient subset. Additionally, this study assumed that medication changes will occur given the presence of an at-risk genotype regardless of other clinical factors, which oftentimes does not happen in clinical practice as treatment is dependent on a multimodal approach that is specific to the patient.

Another limitation of the study was that the projected number of genotype-guided interventions was calculated based on publicly available Caucasian at-risk genotype frequencies which does not take into account genetic variances between ethnic groups. For example, African Americans have a higher probability of carrying a *CYP2C19* loss-of-function variant allele than Caucasians, and African Americans made up approximately 21.3% of our study population.[9] The failure to account for a multiethnic population was due to the difficulty of accurately estimating at-risk genotype frequencies from publicly available data. However, this study only serves as phase one of a two-phase study. Patients were required to donate blood samples to the biorepository to be considered for inclusion. In the subsequent phase, their genetic samples will be preemptively genotyped using a multi-gene panel developed by Tim Wiltshire's laboratory at the UNC Eshelman School of Pharmacy. This will allow us to determine the actual number of immediate genotype-guided interventions that could be made in this catheterization laboratory study population.

We took a very conservative approach in this study to project the genetically-guided interventions in this patient population. We defined a drug as genetically actionable if they had FDA boxed warnings and/or CPIC guidelines that recommended a specific action. However, there are numerous more medications that have pharmacogenomic information in their FDA labelling that are common to the cardiac catheterization laboratory population, such as anti-diabetic agents, proton pump inhibitors, and heart failure drugs.[2, 15] Current genomic information on these agents is limited, with data only providing implications on clinical pharmacology and adverse reactions. However, as more pharmacogenomic data is published, there may be actionable genetically-guided recommendations developed for these drugs, and the number of possible genotype-guided interventions in this population would subsequently increase. Additionally, we only assessed the interventions that could be made within a 6 month period. During the study, it was observed that a significant number of patients were either switched to or initiated on genetically actionable medications beyond the 6 month time frame, although this phenomenon was not formally assessed.

The determination of the clinical benefits from preemptive genotyping in patients earlier on may lead to a considerable decrease in risk of adverse events, hospital admissions, and cost of medical care for the patient and institution. Several studies have been published supporting the use of a preemptive genotyping strategy in patients. Van Driest S, et al. looked at 9,589 individuals who had undergone preemptive pharmacogenomic testing through the Vanderbilt Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) program. The panel-based test identified one or more actionable variants in 91% of the genotyped patients. Using medication exposure data from electronic medical records, the study theorized that reactive genotyping would have generated 14,656 genetic tests.[16] Schildcrout J, et al. examined the prescription frequency of 56 medications with known outcomes influenced by variant alleles in a cohort of 52,942 medical home patients at Vanderbilt University Medical Center (VUMC). The study found that within 5 years, 64.8% of individuals were exposed to at least one medication with an established pharmacogenetic association. Additionally, the study estimated that 383 events, attributed to six medications with severe, well-characterized, genetically linked adverse events, could have been prevented with an effective preemptive genotyping program.[17]

To our knowledge, our study is the first-of-its-kind in evaluating the use of a preemptive genotyping strategy in cardiac catheterization laboratory patients. A significant barrier to the widespread implementation of pharmacogenomic-guided medication therapy is the absence of a clearly defined target population. The results of this study provide evidence that cardiac catheterization patients are a promising target population that may benefit from a preemptive, panel-based genotyping strategy. Although additional analyses are required to determine whether preemptive genotyping should be implemented in cardiac catheterization patients, this study serves as a guide for future research that assess the impact of preemptive genotyping on outcomes and cost, and ultimately, establishing preemptive genotyping as an essential and wide-spread testing methodology that can lead to significant improvements in quality of health care.

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Appendix

Figure 1: Flow diagram of eligibility

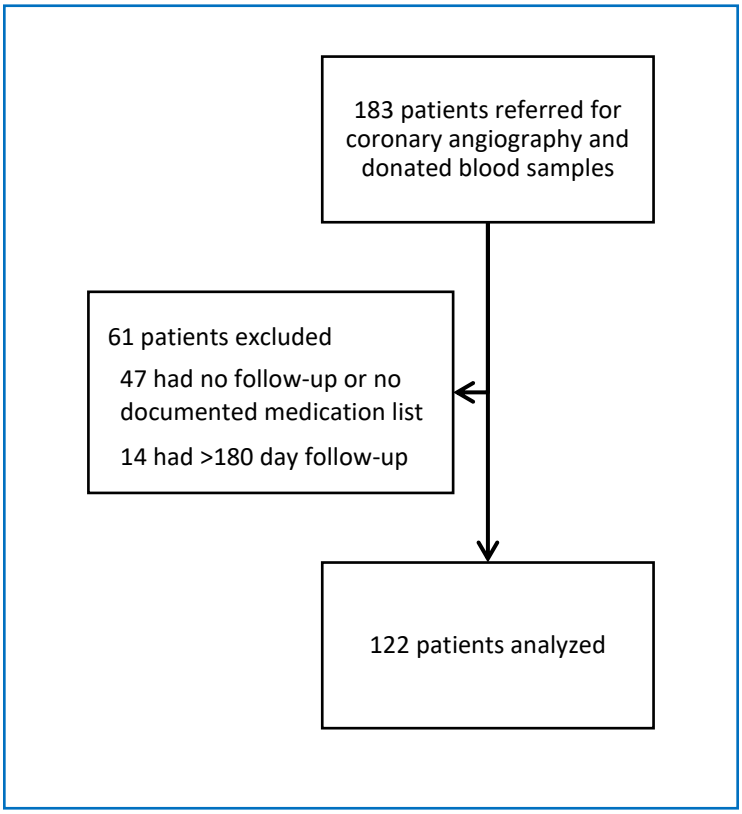

Table 1: Baseline characteristics

Demographics	
Age (Mean ± SD[a])	62.8 ± 10.4
Male	69 (56.6%)
Caucasian	89 (73.0%)
Comorbidities	
Obese (BMI[b] ≥30)	62 (50.8%)
Depression	17 (13.9%)
Hyperlipidemia	78 (63.9%)
Diabetes	41 (33.6%)
Hypertension	95 (77.9%)
Heart failure	21 (17.2%)
CAD History	
Previous MI[c]	22 (18.0%)
Prior PCI[d]	37 (30.3%)
PCI during index visit	46 (37.7%)
Days to first follow-up visit (Mean ± SD)	35.9 ± 34.5

Footnote:

a. Standard deviation
b. Body mass index
c. Myocardial infarction
d. Percutaneous coronary intervention

Table 2: Actionable drug prevalence at discharge or first follow-up

Drug	Prevalence (n)
Amitriptyline	3.3% (4)
Citalopram	6.6% (8)
Clomipramine	0% (0)
Desipramine	0.8% (1)
Doxepin	0% (0)
Escitalopram	1.6% (2)
Fluvoxamine	0% (0)
Imipramine	0.8% (1)
Nortriptyline	0% (0)
Paroxetine	2.5% (3)
Sertraline	4.9% (6)
Trimipramine	0% (0)
Total Antidepressants	20.5% (25)
Carbamazepine	0% (0)
Phenytoin	1.6% (2)
Total Anticonvulsants	1.6% (2)
Allopurinol	2.5% (3)
Clopidogrel	48.4% (59)
Codeine	1.6% (2)
Simvastatin	13.9% (17)
Warfarin	9.0% (11)
Fluorouracil	0% (0)

Table 3: Projected at-risk Caucasian genotype frequencies

Biomarker	Referenced Subgroup	Genotype Frequency	Actionable Drugs
HLA-B[7,8]	*HLA-B*5801* allele carriers	0.8%	Allopurinol
	*HLA-B*1502* allele carriers	0.01%	Carbamazepine, phenytoin
CYP2D6[10]	Ultrarapid metabolizer	1.5%	Antidepressants, codeine
	Intermediate metabolizer	6.5%	Antidepressants, codeine
	Poor metabolizer	7.5%	Antidepressants, codeine
CYP2C19[5,9]	Ultrarapid metabolizer	30.0%	Antidepressants
	Intermediate metabolizer	26.4%	Clopidogrel
	Poor metabolizer	2.5%	Clopidogrel, antidepressants
CYP2C9[8]	Intermediate metabolizer	29.3%	Phenytoin
	Poor metabolizer	3.7%	Phenytoin
SLCO1B1[11]	T/C genotype	21.6%	Simvastatin
	C/C genotype	2.0%	Simvastatin
VKORC1 /CYP2C9[12]	Highly sensitive responders	2.9%	Warfarin
	Sensitive responders	35.4%	Warfarin
DYPD[13]	Partial DPD deficiency	4.0%	Fluorouracil
	DPD deficiency	0.2%	Fluorouracil

Table 4: Sample calculation

Drug	Biomarker	Referenced subgroup(s)	Drug prevalence at discharge of first follow-up	At risk genotype frequency	Projected number of interventions
Clopidogrel	*CYP2C19*	*CYP2C19* intermediate and poor metabolizers	48.4%	28.9%	17[e]
Warfarin	*CYP2C9/VKORC1*	Sensitive/highly sensitive responders	9.0%	38.3%	4
Simvastatin	*SLCO1B1*	C allele carriers	13.9%	23.6%	4

Footnote:

e. Calculation: 0.484*0.289*122 = 17

Table 5: Projected number of interventions at discharge or first follow-up in study population

Study population (n=122)			
Biomarker	**Discharge**	**First Follow-Up**	**Discharge or First Follow-Up**
HLA-B	0 (0.0%)	0 (0.0%)	0 (0.0%)
CYP2D6	0 (0.0%)	0 (0.0%)	0 (0.0%)
CYP2C19	17 (73.9%)	22 (71.0%)	23 (71.9%)
CYP2C9	1 (4.3%)	1 (3.2%)	1 (3.1%)
SLCO1B1	3 (13.0%)	4 (12.9%)	4 (12.5%)
VKORC1/CYP2C9	2 (8.7%)	4 (12.9%)	4 (12.5%)
Total	**23 (100.0%)**	**31 (100.0%)**	**32 (100.0%)**

Figure 2: Distribution of total interventions by gene in study population

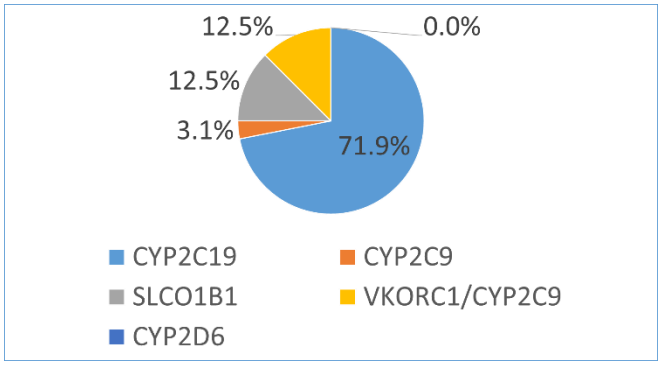

Table 6: Projected annual number of interventions at discharge or first follow-up

Annual UNC catheterization laboratory population (n=2000)		
Biomarker	**First Follow-Up**	**Discharge or First Follow-Up**
HLA-B	0 (0.0%)	0 (0.0%)
CYP2D6	25 (4.6%)	25 (4.4%)
CYP2C19	382 (69.7%)	396 (69.7%)
CYP2C9	12 (2.2%)	12 (2.1%)
SLCO1B1	66 (12.0%)	66 (11.6%)
VKORC1/CYP2C9	63 (11.5%)	69 (12.1%)
Total	**548 (100.0%)**	**568 (100.0%)**

Table 7: Drugs with Pharmacogenomic information in FDA labeling

Drug	Biomarker(s)	Referenced Subgroup(s)	FDA Labeling Change	FDA Blackbox Warning(s)	CPIC Guidelines	Top 200 Prescribed in 2012 (Y/N); Rank(s)	Top 200 Sold ($) in 2012 (Y/N); Rank(s)
Abacavir	HLA-B	HLA-B*5701 allele carriers	Contraindications, Warnings and Precautions	Hypersensitivity reactions: Increased risk for serious to fatal hypersensitivity reactions in HLA-B*5701 allele carriers. Screening for allele prior to therapy initiation is recommended.	Yes (2012 and 2014)	No	No
Allopurinol	HLA-B	HLA-B*5801 allele carriers	No	No	Yes (2013 and 2015)	Yes; 123, 194	No
Amitriptyline	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	Yes (2013)	Yes; 134	No
	CYP2C19	CYP2C19 poor metabolizers	No	No	Yes (2013)		
Arformoterol	UGT1A1	UGT1A1 poor metabolizers	Clinical Pharmacology	No	No	No	No
	CYP2D6	CYP2D6 intermediate or poor metabolizers	Clinical Pharmacology	No	No		
Aripiprazole	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Clinical Pharmacology	No	No	Yes; 92	Yes; 2
Atomoxetine	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology	No	No	No	Yes; 118
Azathioprine	TPMT	TPMT intermediate or poor metabolizers	Clinical Pharmacology, Warnings, Precautions, Drug Interactions, Adverse Reactions, Dosage and Administration	No	Yes (2011 and 2013)	No	No
Boceprevir	IFNL3	IL28B rs12979860 T allele carriers (C/T and T/T genotype)	Clinical Pharmacology	No	Yes (2013)	No	No
Carbamazepine	HLA-B	HLA-B*1502 allele carriers	Boxed Warning, Warnings, Precautions	Dermatological reactions: Increased risk for serious to fatal dermatological reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, in HLA-B*1502 allele carriers. This allele is almost found exclusively in patients with Asian ancestry. Screen genetically at-risk populations prior to therapy initiation and do not treat allele-positive patients unless benefit clearly outweighs risk.	Yes (2013)	No	No
	HLA-A	HLA-A*3101 allele carriers	Warnings	No	No		
Carglumic acid	NAGS	N-acetylglutamate synthase deficient	Indications and Usage, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	No	No	No	No
Carisoprodol	CYP2C19	CYP2C19 poor metabolizers	Use in Specific Populations, Clinical Pharmacology	No	No	No	No
Carvedilol	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions, Clinical Pharmacology	No	No	Yes; 86, 142	No
Celecoxib	CYP2C9	CYP2C9 poor metabolizers	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	No	No	Yes; 76	Yes; 26
Cevimeline	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	No	No	No
Chloroquine	G6PD	G6PD deficient	Precautions	No	No	No	No
Chlorpropamide	G6PD	G6PD deficient	Precautions	No	No	No	No
Citalopram	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology, Warnings, Dosage and Administration		Yes (2015)	Yes; 64, 81	No
Clobazam	CYP2C19	CYP2C19 poor metabolizers	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	No	No	No	No
Clomipramine	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	Yes (2013)	No	No
	CYP2C19	CYP2C19 poor metabolizers	No	No	Yes (2013)		

Clopidogrel	CYP2C19	CYP2C19 intermediate or poor metabolizers	Boxed Warning, Dosage and Administration, Warnings and Precautions, Clinical Pharmacology	Diminished effectiveness: Diminished effect of clopidogrel on platelet function in CYP2C19 poor metabolizers and exhibition of higher cardiovascular event rates in poor metabolizers who also have acute coronary syndrome or who are undergoing percutaneous coronary intervention as compared to normal metabolizers. Consider alternative treatment or treatment strategies in poor metabolizers.	Yes (2011 and 2013)	Yes; 55	Yes; 13
Clozapine	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology	No	No	No	No
Codeine	CYP2D6	CYP2D6 ultra-rapid metabolizers	Boxed Warnings, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information	Ultra-rapid metabolism of codeine to morphine: Occurrence of respiratory depression and death in children receiving codeine after tonsillectomy and/or adenoidectomy with evidence of being a CYP2D6 ultra-rapid metabolizer.	Yes (2012 and 2014)	No	No
Dapsone	G6PD	G6PD deficient	Warnings and Precautions, Use in Specific Populations, Patient Counseling Information, Adverse Reactions, Overdosage	No	No	No	No
Darifenacin	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions, Clinical Pharmacology	No	No	No	No
Desipramine	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	Yes (2013)	No	No
	CYP2C19	CYP2C19 poor metabolizers	No	No	Yes (2013)		
Dexlansoprazole	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions, Clinical Pharmacology	No	No	Yes; 182	Yes; 80
Dextromethorphan quinidine	CYP2D6	CYP2D6 poor metabolizers	Warnings and Precautions, Clinical Pharmacology	No	No	No	No
Diazepam	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology	No	No	Yes; 122, 196	No
Divalproex	POLG	POLG mutation positive	Boxed Warning, Contraindications, Warnings and Precautions	Acute liver failure: Increased risk of valproate-induced hepatic failure and deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA polymerase gamma (POLG) gene (eg, Alpers-Huttenlocher syndrome). Use is contraindicated in patients with mitochondrial disorders caused by POLG mutations and children <2 years with suspected POLG-related disorder. In patients ≥2 years with suspected POLG-related disorder, only use after failure of other anticonvulsants with close monitoring for acute liver injury. Conduct POLG mutation screening in accordance with current clinical practice.	No	No	No
Doxepin	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology		Yes (2013)	No	No
	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology		Yes (2013)	No	No
Drospirenone/ Ethinyl Estradiol	CYP2C19	CYP2C19 intermediate metabolizers	Clinical Pharmacology		No	No	No
Eliglustat	CYP2D6	CYP2D6 ultrarapid, intermediate or poor metabolizers	Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, Use in Specific Populations, Drug Interactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies	No	No	No	No
Eltrombopag	F5	Factor V Leiden carriers	Warnings and Precautions		No	No	No
	SERPINC1	Antithrombin III deficient	Warnings and Precautions		No	No	No
Erythromycin/Sulfisoxazole	G6PD	G6PD deficient	Warnings and Precautions	No	No	No	No
Esomeprazole	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions, Clinical Pharmacology	No		Yes; 12**	Yes; 1**

Escitalopram	CYP2C19	CYP2C19 poor metabolizers	No	No	Yes (2015)	Yes; 72, 128, 153	Yes; 81, 113, 136
Fesoterodine	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions, Clinical Pharmacology	No	No	No	No
Fluorouracil	DPYD	DPD deficient	Contraindications, Warnings, Patient Information	No	Yes (2014, 2013)	No	No
Fluoxetine	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology, Warnings, Precautions	No	No	Yes; 57	No
Flurbiprofen	CYP2C9	CYP2C9 poor metabolizers	Clinical Pharmacology	No	No	No	No
Fluvoxamine	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions	No	Yes (2015)	No	No
Galantamine	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology	No	No	No	No
Glimepiride	G6PD	G6PD deficient	Warning and Precautions, Adverse Reactions	No	No	No	No
Glipizide	G6PD	G6PD deficient	Precautions	No	No	No	No
Glyburide	G6PD	G6PD deficient	Precautions	No	No	No	No
Iloperidone	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Warnings and Precautions,Drug Interactions, Clinical Pharmacology	No	No	No	No
Imipramine	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	Yes (2013)	No	No
	CYP2C19	CYP2C19 poor metabolizers	No	No	Yes (2013)	No	No
Indacaterol	UGT1A1	UGT1A1-*28 allele homozygotes	Clinical Pharmacology	No	No	No	No
Isosorbide dinitrate and Hydralazine	NAT1-2	Slow acetylators	Clinical Pharmacology	No	No	No	No
Ivacaftor	CFTR	CFTR G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation carriers, F508del mutation homozygotes	Indications and Usage Adverse Reactions Use in Specific Populations Clinical Pharmacology Clinical Studies	No	Yes (2014)	No	No
Lansoprazole	CYP2C19	CYP2C19 intermediate or poor metabolizers	Drug Interactions	No	No	No**	No**
Lenalidomide	del (5q)	Chromosome 5q deletion positive	Boxed Warning, Indications and Usage, Adverse Reactions, Use in Specific Populations, Clinical Studies	Hematologic toxicity (grade 3/4): Lenalidomide can cause neutropenia and thrombocytopenia in 80% of patients with del 5q myelodysplastic syndrome. May require dose reductions and/or delays. Monitor CBC weekly for first 8 weeks and at least monthly thereafter in patients being treated for del 5q myelodysplastic syndromes. Use of blood product support and/or growth factors may be needed.	No	No	Yes; 120
Lomitapide	LDLR	LDLR mutation homozygotes (homozygous familial hypercholesterolemia)	Indication and Usage, Warnings and Precautions, Adverse Reactions, Clinical Studies	No	No	No	No
Mafenide	G6PD	G6PD deficient	Warnings Adverse Reactions	No	No	No	No
Methylene blue	G6PD	G6PD deficient	Precautions	No	No	No	No
Metoclopramide	CYB5R1-4	NADH cytochrome b5 reductase deficient	Precautions	No	No	No	No
Metoprolol	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology	No	No	Yes; 16, 32, 69 106, 183, 186	Yes; 145
Mipomersen	LDLR	LDLR mutation heterozygotes and homozygotes (heterozygous and homozygous familial hypercholesterolemia)	Boxed Warning, Indications and Usage, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies	Transaminase elevation: In clinical trials in patients with homozygous familial hypercholesterolemia, 12% of patients treated with mipomersen had at least 1 elevation in ALT at least 3 times the upper limit of normal (ULN); Increase in hepatic fat with or without concomitant transaminase elevations: In trials in patients with heterozygous familial hypercholesterolemia and hyperlipidemia, the median absolute increase in hepatic fat was 10% (from 0% at baseline) after 26 weeks of treatment. Hepatic steatosis is a risk factor for advanced liver disease, including steatohepatitis and cirrhosis.	No	No	No

Modafinil	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology, Precautions	No	No	No	Yes; 137
Mycophenolic Acid	HPRT1	HGPRT deficient	Warnings and Precautions	No	No	No	No
Nalidixic Acid	G6PD	G6PD deficient	Precautions, Adverse Reactions	No	No	No	No
Nefazodone	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	No	No	No
Nitrofurantoin	G6PD	G6PD deficient	Warnings, Adverse Reactions	No	No	No	No
Norfloxacin	G6PD	G6PD deficient	Precautions, Adverse Reactions	No	No	No	No
Nortriptyline	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	Yes (2013)	No	No
Omeprazole	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions	No	No	Yes; 28, 29, 45, 46, 131**	No**
Pantoprazole	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology	No	No	Yes; 121**	No**
Paroxetine	CYP2D6	CYP2D6 extensive metabolizers	Drug Interactions	No	Yes (2015)	Yes; 143	No
PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate, and Ascorbic Acid (Vitamin C)	G6PD	G6PD deficient	Warnings and Precautions	No	No	No**	No**
Peginterferon alfa-2a	IFNL3	IL28B rs12979860 T allele carriers (C/T and T/T genotype)	Clinical Pharmacology, Efficacy	No	Yes (2013)	No	No
Peginterferon alfa-2b	IFNL3	IL28B rs12979860 T allele carriers (C/T and T/T genotype)	Clinical Pharmacology, Efficacy	No	Yes (2013)	No	No
Pegloticase	G6PD	G6PD deficient	Contraindications Patient Counseling Information	No	No	No	No
Perphenazine	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology, Precautions	No	No	No	No
Phenytoin	HLA-B	HLA-B*1502 allele carriers	Warnings	No	Yes (2014)	No	No
	CYP2C9	CYP2C9 poor metabolizers	No	No	Yes (2014)		
Pimozide	CYP2D6	CYP2D6 poor metabolizers	Precautions, Dosage and Administration	No	No	No	No
Prasugrel	CYP2C19	CYP2C19 poor metabolizers	CYP2C19 poor metabolizers	No	No	No	Yes; 184
	CYP2C9	CYP2C9 variant carriers	Use in Specific Populations Clinical Pharmacology Clinical Studies	No	No		
	CYP3A5	CYP3A5 variant carriers	Use in Specific Populations Clinical Pharmacology Clinical Studies	No	No		
	CYP2B6	CYP2B6 variant carriers	Use in Specific Populations Clinical Pharmacology Clinical Studies	No	No		

Pravastatin	LDLR	LDLR mutation heterozygotes and homozygotes (heterozygous and homozygous familial hypercholesterolemia)	Indications and Usage, Use in Specific Populations, Clinical Studies	No	No	Yes; 25, 136	No
Primaquine	G6PD	G6PD deficient	Warnings, Precautions, Adverse Reactions	No	No	No	No
Probenecid	G6PD	G6PD deficient	Adverse Reactions	No	No	No	No
Propafenone	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Warnings and Precautions, Clinical Pharmacology	No	No	No	No
Propranolol	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology	No	No	No	No
Protriptyline	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	No	No	No
Quinidine	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	No	No	No
Quinine Sulfate	G6PD	G6PD deficient	Contraindications	No	No	No	No
	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions	No	No		
Rabeprazole	CYP2C19	CYP2C19 poor metabolizers	Drug Interactions, Clinical Pharmacology	No	No	No	Yes; 69
Rifampin, Isoniazid, and Pyrazinamide	NAT1-2	Slow acetylators (inactivators)	Clinical Pharmacology, Adverse Reactions	No	No	No	No
Risperidone	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology	No	No	Yes; 138	Yes; 141
Ribaviran	IFNL3	IL28B rs12979860 T allele carriers (C/T and T/T genotype)	No	No	Yes (2013)	No	No
Sertraline	CYP2C19	CYP2C19 poor metabolizers	No	No	Yes (2015)	Yes; 36, 54, 79	No
Simeprevir	IFNL3	IL28B rs12979860 T allele carriers	Clinical Pharmacology, Clinical Studies	No	No	No	No
Simvastatin	SLCO1B1	rs4149056 C allele carriers (T/C and C/C genotype)	No	No	Yes (2012 and 2014)	Yes; 6, 42, 58, 63, 85, 140, 141	No
Sodium Nitrite	G6PD	G6PD deficient	Warnings and Precautions	No	No	No	No
Sodium phenylacetate and Sodium Benzoate	NAGS, CPS1, ASS1, OTC, ASL, ABL2	Urea cycle enzyme deficient	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Overdosage, Clinical Pharmacology, Clinical Studies	No	No	No	No
Sofosbuvir	IFNL3	IL28B rs12979860 T allele carriers (non-C/C genotype)IL28B	Clinical Studies	No	No	No	No
Succimer	G6PD	G6PD deficient	Clinical Pharmacology	No	No	No	No
Succinylcholine	BCHE	Atypical homozygous carriers	Adverse Reactions, Warnings and Precautions	No	No	No	No
Sulfadiazine	G6PD	G6PD deficient	Warnings	No	No	No	No
Sulfamethoxazole/Trimethoprim	G6PD	G6PD deficient	Precautions	No	No	No	No

Sulfasalazine	G6PD	G6PD deficient	Precautions	No	No	No	No
Tacrolimus	CYP3A5	CYP3A5 intermediate or extensive metabolizers	No	No	Yes (2015)	No	Yes; 165
Telaprevir	IFNL3	IL28B rs12979860 T allele carriers (C/T and T/T genotype)	Clinical Pharmacology, Clinical Studies	No	Yes (2013)	No	Yes; 39
Terbinafine	CYP2D6	CYP2D6 poor metabolizers	Drug Interactions	No	No	No	No
Tetrabenazine	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology	No	No	No	No
Thioridazine	CYP2D6	CYP2D6 poor metabolizers	Contraindications, Warnings, Precautions	No	No	No	No
Ticagrelor	CYP2C19	CYP2C19 poor metabolizers	Clinical Studies	No	No	No	No
Tolterodine	CYP2D6	CYP2D6 poor metabolizers	Warnings and Precautions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology	No	No	No	Yes; 108
Tramadol	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology	No	No	Yes; 52, 83, 88	No
Trimipramine	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	Yes (2013)	No	No
	CYP2C19	CYP2C19 ultrarapid and poor metabolizers	No	No	Yes (2013)		
Valproic Acid	POLG	POLG mutation positive	Boxed Warning, Contraindications, Warnings and Precautions	Acute liver failure: Increased risk of valproate-induced hepatic failure and deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA polymerase gamma (POLG) gene (eg, Alpers-Huttenlocher syndrome). Use is contraindicated in patients with mitochondrial disorders caused by POLG mutations and children <2 years with suspected POLG-related disorder. In patients ≥2 years with suspected POLG-related disorder, only use after failure of other anticonvulsants with close monitoring for acute liver injury. Conduct POLG mutation screening in accordance with current clinical practice.	No	No	No
	NAGS, CPS1, ASS1, OTC, ASL, ABL2	Urea cycle enzyme deficient	Contraindications, Warnings and Precautions	No	No		
Venlafaxine	CYP2D6	CYP2D6 poor metabolizers	Precautions	No	No	Yes; 90	No
Voriconazole	CYP2C19	CYP2C19 intermediate or poor metabolizers	Clinical Pharmacology	No	No	No	No
Vortioxetine	CYP2D6	CYP2D6 poor metabolizers	Dosage and Administration, Clinical Pharmacology	No	No	No	No
Warfarin	CYP2C9	CYP2C9 intermediate or poor metabolizers	Dosage and Administration Drug Interactions Clinical Pharmacology	No	Yes (2011 and 2013)	Yes; 18, 89	No
	VKORC1	VKORC1 A allele carriers	Dosage and Administration Clinical Pharmacology	No	Yes (2011 and 2013)		
	PROS	Protein S deficient	Warnings and Precautions	No	No		
	PROC	Protein C deficient	Warnings and Precautions	No	No		

**OTC Options Available and not accounted for